Abdominal adipose tissue is associated with alterations in tryptophan-kynurenine metabolism and markers of systemic inflammation in people with HIV

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Summary: Abdominal fat was associated with activation of the pro-inflammatory pathway of kynurenine metabolism with reduction of anti-inflammatory molecules and increase in systemic inflammation. Hence, dysregulation of kynurenine metabolism associated with abdominal fat accumulation may be a potential source of inflammation in HIV infection.

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Abstract

Background: While both adipose tissue accumulation and tryptophan metabolism alterations are features of HIV infection, their interplay is unclear. We investigated associations between abdominal adipose tissue, alterations in kynurenine pathway of tryptophan metabolism, and systemic inflammation in people with HIV (PWH).

Methods: 864 PWH and 75 uninfected controls were included. Plasma samples were collected and analyzed for kynurenine metabolites, neopterin, high-sensitivity CRP (hs-CRP), lipids. Regression models were used to test associations in PWH.

Results: PWH had higher kynurenine-to-tryptophan ratio than uninfected individuals (p-value < 0.001). In PWH, increase in waist-to-hip ratio was associated with higher kynurenine-to-tryptophan ratio (p-value 0.009) and quinolinic-to-kynurenic acid ratio (p-value 0.006) and lower kynurenic acid concentration (p-value 0.019). Quinolinic-to-kynurenic acid ratio was associated with higher hs-CRP (p-value < 0.001) and neopterin concentrations (p-value <0.001), while kynurenic acid was associated with lower hs-CRP (p-value 0.025) and neopterin concentrations (p-value 0.034).

Conclusion: In PWH increase in abdominal adipose tissue was associated with increased quinolinic-to-kynurenic acid ratio, suggesting activation of pro-inflammatory pathway of kynurenine metabolism, with reduction of anti-inflammatory molecules, and increase in systemic inflammation. Our results suggest dysregulation of kynurenine metabolism associated with abdominal fat accumulation to be a potential source of inflammation in HIV infection.

Introduction

Despite the introduction of less metabolic harmful combination antiretroviral therapy (cART) regimens, abdominal accumulation of adipose tissue is still a distinct feature in PWH [1]. Furthermore, an important role for new generation antiretroviral agents, especially integrase inhibitors, in weight gain has recently been proposed [2–5]. While the cardiometabolic consequences of central obesity are well described, its impact on markers of systemic inflammation is less clear [6]. However, recent studies have suggested adipose tissue to have a critical role in pro-inflammatory cells dynamics [7].

Tryptophan is an essential amino acid involved in protein and serotonin synthesis. Tryptophan also represents the unique substrate for the synthesis of kynurenine and kynurenine metabolites, collectively called kynurenines [8]. The first and rate limiting step of this pathway is mainly catalyzed by the enzyme, indoleamine 2,3-dioxygenase 1 (IDO-1). IDO-1 is expressed in several tissues, including adipose tissue, and its activity is induced by pro-inflammatory cytokines [8]. Kynurenine is then further metabolized by kynurenine aminotransferase and kynurenine monooxygenase, to form either kynurenic acid or alternatively, 3-hydroxy-kynurenine and, eventually, quinolinic acid [8,9] (Supplementary Figure 1). Within the adipose tissue kynurenine monooxygenase has been described to be mainly expressed in resident macrophages, and not in primary adipocytes [10]. Accordingly, in presence of macrophage activation, the catabolism of kynurenine shifts from adipocytes toward macrophages leading to reduction in the production of kynurenic acid in favor of quinolinic acid (i.e., increasing the quinolinic-to-kynurenic acid ratio) [10]. Kynurenic acid has been reported to have anti-inflammatory properties, to beneficially regulate energy homeostasis and

lipid metabolism in the adipose tissue and has been proposed as a potential therapeutic agent in obesity in uninfected individuals [11–13].

While IDO-1 activity is known to be increased in PWH [14,15], the possible impact of fat accumulation in HIV infection on the kynurenine pathway of tryptophan metabolism is unknown. The association of kynureine metabolites with fat accumulation [16,17] and CVD risk [18–20] has been the subject of increasing interest in uninfected individuals, but remains largely unexplored in PWH [21].

In the present study we aimed to investigate the complex interplay between fat accumulation, alterations in the kynurenine pathway of tryptophan metabolism, and systemic inflammation, in the context of HIV infection. For this purpose, in PWH we: i) investigated possible associations between waist-to-hip ratio and kynurenine-to-tryptophan ratio, quinolinic-to-kynurenic acid ratio and kynurenine metabolites, ii) investigated possible associations of quinolinic acid, kynurenic acid, and quinolinic-to-kynurenic acid ratio with markers of systemic inflammation, iii) exploratively, assessed possible associations between kynurenine metabolites and serum lipids, hypertension, and diabetes, respectively.

Methods

Study population

PWH were recruited from the Copenhagen Comorbidity in HIV infection (COCOMO) study. The COCOMO study is an ongoing longitudinal, observational study with the aim of assessing the burden of non-AIDS comorbidities in PWH. Of the 1099 participants in the COCOMO study, 864 PWH ≥ 40 years old and with available measurements of tryptophan, kynurenine, and kynurenine metabolites were included in the present study. 75 uninfected controls from the background population were also included as a part of the COCOMO study.

Procedures for recruitment and data collection for COCOMO have been described elsewhere [22]. Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350). Written informed consent was obtained from all participants.

Clinical and biochemical assessments

Structured questionnaires were used in COCOMO to collect information about demographics, physical activity, smoking, and lipid lowering therapy [22].

Data regarding HIV infection were obtained from complete review of medical charts [22].

All physical examinations were performed by trained clinic staff, as previously described [22]. According to Joint National Committee (JNC) guidelines, hypertension was defined as anti-hypertensive treatment and/or as having ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic BP values [23]. Diabetes was defined as minimum one of: anti-diabetic treatment, non-fasting venous plasma glucose ≥ 11.1 mmol/l, and HbA1c ≥ 48mmol/mol.

Height, weight, hip, and waist measurements and body mass index (BMI) calculations were performed according to WHO guidelines[24].

Non-fasting venous blood was collected and analyzed for high-sensitivity CRP (hs-CRP), total cholesterol, low- and high-density lipoprotein (LDL and HDL), and triglycerides (TG). Blood samples were analyzed at Herlev University Hospital, Copenhagen[22].

Plasma samples were collected and stored at -80°C until use. Plasma was analyzed for tryptophan, kynurenine, kynurenine metabolites, and neopterin concentrations by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described [25]. These analyses were performed at BEVITAL (www.bevital.no).

The ratio between kynurenine and tryptophan was used as a measure of IDO-1 activity and the quinolinic-to-kynurenic acid ratio as a measure of the macrophage dependent kynurenine metabolism (Supplementary Figure 1). Plasma concentration of neopterin was used as a marker of macrophage activation. In the interest of clarity kynurenine-to-tryptophan ratio and quinolinic-to-kynurenic acid ratio were multiplied for a factor of 1000 and 10, respectively.

Statistical analyses

Continuous variables were reported as median and interquartile range [IQR] and categorical variables as frequency and percentage (%). PWH and uninfected controls were compared with t-tests or Mann Whitney U test for continuous data with normal or non-normal distribution, respectively, and chi square/Fisher's tests for categorical data.

In PWH, multivariable linear regression models were used to assess the association of waist-to-hip ratio and kynurenine-to-tryptophan ratio and kynurenine metabolites. Covariates included in the

base model were age, sex, smoking status, origin, and BMI. Kynurenine concentration was also added to the model when using quinolinic acid, kynurenic acid, and quinolinic-to-kynurenic acid ratio as dependent variables.

The associations of quinolinic acid, kynurenic acid, quinolinic-to-kynurenic acid ratio with markers of systemic inflammation and macrophage activation were also explored. In these models, hs-CRP and neopterin concentrations were used as dependent variables. Confounders included in the models were age, sex, smoking status, origin, BMI, and kynurenine concentration.

In sensitivity analyses the base model was further adjusted for renal function (eGFR) and physical activity (inactive, moderately inactive, moderately active, and very active).

In exploratory analyses, when assessing the association between lipids and kynurenine metabolites in PWH, the base model was further adjusted for current lipid lowering therapy. In these analyses, due to lack of a clear pre-defined hypothesis, p-values were also adjusted for multiple testing (Bonferroni Holm´s method). Finally, associations between hypertension, diabetes, and kynurenine metabolites were explored using logistic regression models adjusted for age, sex, smoking status, origin, and BMI.

In regression analyses, the concentrations of kynurenine metabolites were log-transformed to better fit the models and estimates are presented as changes in percentage to facilitate the interpretation of the results.

All statistical analyses were performed using R statistical software version 3.4.1 (Foundation for Statistical Computing, Vienna, Austria). The following packages were used (alphabetical order): *“compareGroups”, “ggplot2”, “jtools”*, and *“Publish”.*

Results

Demographic characteristics

864 PWH and 75 uninfected controls from the COCOMO study were included. Characteristics of the participants are shown in Table 1.

Kynurenines metabolism and immune activation in PWH and uninfected controls

PWH had higher kynurenine-to-tryptophan ratio and kynurenine concentration compared to uninfected controls (25.5 vs 22.2, p-value < 0.001 and 1.6 vs 1.4 µmol/L, p-value < 0.001, respectively). No difference in tryptophan concentration, quinolinic-to-kynurenic acid ratio, quinolinic acid, kynurenic acid, and 3-hydroxyanthranilic acid concentrations was found between PWH and controls after adjusting for confounders (Table 2). PWH had higher hs-CRP and neopterin concentrations both before and after adjusting for confounders (Table 2).

Association of waist-to-hip ratio with kynurenine metabolites and systemic inflammation in PWH

In PWH, 0.5-unit increase in waist-to-hip ratio was associated with 31 % higher kynurenine-to-tryptophan ratio, and 44 % higher quinolinic-to-kynurenic acid ratio, increments that were reduced to 19% and 33%, respectively, after adjusting for confounders (all p-values < 0.01, Table 3). 0.5-unit increase in waist-to-hip ratio was associated with higher concentrations of hs-CRP and neopterin, and lower lower kynurenic acid concentration (Table 3).

In sensitivity analyses, all the above associations were not modified by further adjusting the models for renal function (eGFR) and physical activity (data not shown).

Association of quinolinic acid and kynurenic acid with markers of systemic inflammation in PWH

In PWH quinolinic-to-kynurenic acid ratio and quinolinic acid concentration were associated with higher hs-CRP (adjusted β coefficient (aβ) 0.44 [0.25;0.64], p-value and aβ 0.79 [0.45;1.13], respectively; all p-values < 0.001) and higher neopterin concentrations (aβ 0.23 [0.18;0.29] and aβ 0.55 [0.46;0.64], respectively; all p-values < 0.001) (Figure 1). In contrast, kynurenic acid concentration was associated with lower hs-CRP (aβ -0.28 [-0.52; -0.03], p-value 0.025) and neopterin concentrations (adjusted β -0.07 [-0.14; -0.01], p-value 0.034) (Figure 1).

In sensitivity analyses, all the above associations were maintained after further adjusting the models for waist-to-hip ratio or renal function (eGFR) (data not shown).

Association of kynurenine metabolism with lipids levels, hypertension, diabetes, and duration of cART in PWH

In PWH, increase in kynurenine-to-tryptophan ratio, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid were associated with lower cholesterol and LDL plasma levels after adjusting for confounders (age, sex, BMI, smoking status, origin, and anti-dyslipidemia treatment) (Figure 2). Increase in kynurenine-to-tryptophan ratio, kynurenine, and quinolinic acid were also associated with lower HDL levels and increases in 3-hydroxykynurenine and tryptophan were associated with lower and higher levels of triglycerides, respectively (Figure 2). After adjusting for multiple testing, 3-hydroxyanthranilic acid, 3-hydroxykynurenine, kynurenine, and quinolinic acid remained associated with lower total cholesterol and LDL, and kynurenine-to-tryptophan ratio remained associated with lower total cholesterol, but not LDL.

No associations were found between kynurenine metabolites and hypertension and diabetes, respectively (Supplementary Table 1).

In explorative linear regression models adjusted for age, sex, origin, BMI, and smoking, no associations were found between cumulative duration of cART and kynurenine (p-value 0.228), tryptophan (p-value 0.855), kynurenine-to-tryptophan ratio (p-value 0.222), quinolinic acid (p-value 0.557), kynurenic acid (p-value 0.089), and quinolinic-to-kynurenic acid (p-value 0.375).

Discussion

In the present study we found well-treated PWH to have increased levels of several kynurenines compared to uninfected controls. Furthermore, in PWH increase in waist-to-hip ratio was associated with a shift from the production of kynurenic acid towards quinolinic acid which, in turn, was associated with increase in markers of systemic inflammation and macrophage activation. Accordingly, we observed a strong association between systemic inflammation and abdominal adipose tissue in the context of HIV infection. Finally, we found that in PWH, kynurenines were associated with lower concentration of circulating lipids which is in contrast to previous observations in uninfected individuals [19,26].

While the incidence of lipoatrophy has declined with the reduction in the use of old generation cART, abdominal obesity is still observed in PWH in the contemporary cART era [1]. Accordingly, recent studies suggested modern cART regimens, particularly integrase inhibitors, to be associated with weight gain [2–4]. Thus, investigating the impact of fat accumulation on immunomodulatory molecule is of primary importance. Adipose tissue distribution and its metabolic consequences have been widely studied in the context of HIV infection [1,6], but studies on adipose tissue-related immune functions, especially macrophage infiltration, are scarce and results contradicting [27,28]. In uninfected persons, obesity has been associated with increased IDO-1 activity [16]. Accordingly, we observed positive association of kynurenine-to-tryptophan ratio with waist-to-hip ratio. Local inflammation, previously shown to accompany abdominal fat accumulation, has been suggested to be a key determinant in IDO-1 activity associated with obesity [16,17]. However, gut microbiome alterations (i.e. bacterial translocation and IDO-like enzymes producing bacteria) have also been associated with both increased activity of the kynurenine-pathway of tryptophan metabolism and

adipose tissue accumulation. In particular, previous studies described bacterial translocation-associated increase in LPS levels to be able induce both IDO-1 activity [29,30] and obesity [31]. We speculated that the association between kynurenine-to-tryptophan ratio and waist-to-hip ratio may be the result of a complex interplay between endogenous (e.g. obesity-associated adipose tissue local inflammation) and exogenous (bacterial translocation and dysbiosis) stimuli.

In the context of HIV infection, infiltrating macrophages, rather than adipocytes, are the primary source of pro-inflammatory molecules within the adipose tissue and have been proposed as a possible important contributor to systemic inflammation [27]. IDO-1 catalyzes the formation of kynurenine, which is further metabolized into either kynurenic acid, catalyzed by kynurenine aminotransferase, or, after several steps, to quinolinic acid, via kynurenine monooxygenase [8]. Within the adipose tissue, kynurenine aminotransferase is normally expressed in adipocytes and pre-adipocytes, whereas kynurenine monooxygenase is mainly expressed in infiltrating pro-inflammatory macrophages [10], and is a key enzyme in maintaining the physiological balance between quinolinic acid and kynurenic acid production [9]. Quinolinic-to-kynurenic acid ratio has been used as an indirect measure of the balance between these two metabolic branches [8,9]. Increased activity of kynurenine monooxygenase has been linked to morbid obesity, possibly due to macrophage infiltration in the adipose tissue [10]. Interestingly, in the context of HIV infection, abdominal adipose tissue may affect the balance between kynurenine aminotransferase and kynurenine monooxygenase activity. In particular, increase in waist-to-hip ratio was associated with increase in quinolinic-to-kynurenic acid ratio, which may reflect an increase in macrophage infiltration. Consequently, a shift towards the kynurenine monooxygenase-mediated pathway of kynurenine metabolism in macrophages may occur in the abdominal adipose tissue of PWH, thus causing reduction of kynurenic acid concentration in favor of the production of quinolinic acid.

Accordingly, we found a negative association between waist-to-hip ratio and kynurenic acid concentration in PWH.

Kynurenic acid has previously been proposed to have important and beneficial effect on adipose tissue environment, acting as anti-inflammatory and tissue protective modulator, by activating the Gpr35 receptor [12,13]. The negative association between kynurenic acid concentrations and both systemic inflammation and macrophage activation found in PWH supports this hypothesis. On the other hand, quinolinic acid is known to impose oxidative stress and inflammatory responses [32] and was positively associated with hs-CRP and neopterin in the present study. Taken together our results suggest that the reduction in kynurenic acid levels in favor of quinolinic acid production found to be associated with abdominal fat accumulation may be an important contributor to the pro-inflammatory environment in adipose tissue in PWH.

While the association between kynurenines and adverse immunological outcome is well described in HIV infection [14,15], less is known about the role of kynurenine and kynurenine metabolites in non-AIDS associated comorbidities [21,33]. In uninfected individuals IDO-1 activity has been associated with increase in lipids levels and other CVD risk factors [19,26]. One recent study reported a relationship between alterations of kynurenines and atherosclerosis in PWH [21]. In exploratory analyses we set out to investigate possible associations between kynurenines with lipids levels in PWH. In contrast to previous results in uninfected individuals, that showed associations with adverse lipid profile [19,26], we found increase in concentrations of kynurenines to be associated with lower total, LDL, and HDL cholesterol levels in PWH. We hypothesized that the inverse associations of kynurenines with both LDL and HDL found in HIV infection may suggest an effect of kynurenines on lipids synthesis. Interestingly, previous studies described 3-

hydroxyanthranilic acid to have a potent lipid-lowering and atheroprotective effect in murine models, supposedly as a result of a lipid-modifying effect [34,35]. We speculated that this effect may be a consequence of conditions characterized by high levels of kynurenine metabolites, such as following exogenous administration [34] or increase in IDO-1 activity due pro-inflammatory environment, known to occur in HIV infection. Further studies are needed to investigate the effect of kynurenine metabolites on lipid metabolism in HIV infection and their possible role as therapeutic targets.

The present study has limitations. Due to cross-sectional design, no conclusion on causality can be drawn. Furthermore, clinical data for uninfected controls were not available. This prevented us from evaluating possible interactions between HIV infection and abdominal adipose tissue on kynurenine metabolites concentrations. Finally, kynurenines concentrations were measured systemically, and adipose tissue biopsies were not available to confirm our hypotheses. Thus, while we described kynurenines concentrations and ratios to be associated with abdominal adipose tissue, we could not account for kynurenines production possibly taking place in other organs.

In conclusion, results from the present study indicate that abdominal fat is associated with higher activity of kynurenine metabolism via the pro-inflammatory kynurenine monooxygenase mediated pathway, with reduction in anti-inflammatory molecules and with higher levels of systemic inflammation in PWH. Taken together, our findings suggest central adipose tissue to be accompanied by increase in macrophage infiltration and activation and to be a primary source of chronic low-grade inflammation in the context of HIV infection. Due to increasing evidence suggesting an association between modern generation cART and weight gain, interventional studies

are warranted to address accumulation and distribution of adipose tissue with the prospect to prevent systemic inflammation and potential harmful complications on cardiometabolic health.

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Conflict of interest

MG: unrestricted travel grants from Gilead; PMU: no conflict of interest; MT: no conflict of interest; AM: Honoraria, lecture fees, and travel support from ViiV and Gilead; AML: no conflict of interest; HU: no conflict of interest; ØM no conflict of interest; JL: No conflict of interests; SDN: Unrestricted research grants from Novo Nordisk Foundation, Lundbeck Foundation, Augustinus Foundation, Rigshospitalet Research Council. Travelling grants from Gilead and GSK/ViiV. Advisory board activity for Gilead and GSK/ViiV.

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Tables

Table 1

Characteristics	PWH n = **864**	Controls n = **75**
Age, median [iqr]	52.0 [47.0, 60.4]	59.8 [51.6, 67.1]
Sex, male, n (%)	731 (84.6)	53 (70.7)
BMI, kg/m^2, median [iqr]	24.6 [22.4, 27.3]	-
Origin, n (%)		
Scandinavian	640 (75.3)	-
Other EU	99 (11.6)	-
Middle East	10 (1.2)	-
Other	101 (11.9)	-
HIV transmission mode, n (%)		
Heterosexual	203 (23.7)	-
IDU	12 (1.4)	-
MSM	586 (68.5)	-
Other	54 (6.3)	-
Current CD4, cells/µl, median [iqr]	670 [510, 880]	-
CD4 nadir < 200 cells/ µl, yes, % (n)	378 (44.7)	-
Current viral load < 50, % (n)	815 (95.1)	-
cART, yes, % (n)	846 (98.4)	-
Cumulation cART duration, years, median [iqr]	13.3 [6.5, 18.0]	
Status smoke, n (%)		-
Current smoker	238 (28.2)	-
Ex-smoker	325 (38.6)	-
Never smoker	280 (33.2)	-
Waist-to-hip ratio, median [iqr]	0.9 [0.9, 1.0]	-
Chol, mmol/l, median [iqr]	4.9 [4.2, 5.7]	-
LDL, mmol/l, median [iqr]	2.8 [2.2, 3.4]	-
HDL, mmol/l, median [iqr]	1.1 [0.9, 1.5]	-
TG, mmol/l, median [iqr]	1.8 [1.2, 2.7]	-
Anti-dyslipidemic treatment, yes, n (%)	133 (16.4)	-
eGFR, ml/min/1,73 m2, median [iqr]	87.8 [76.8, 97.5]	-
Hypertension, yes, % (n)	382 (48.0)	-
Diabetes, yes, % (n)	42 (5.1)	-

Abbreviations: PWH, people with HIV; BMI, body mass index; IDU, intravenous drug use; MSM, male to male sex; cART, combination antiretroviral treatment; Chol, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; eGFR, estimated glomerular filtration rate

Table 2. Differences in kynurenines and inflammatory markers between PWH and uninfected controls

Variable median [iqr]	**PWH n = 864**	**Controls n = 75**	**p-value**	**Adjusted p-value**
Kynurenine-to-tryptophan ratio	25.5 [21.6, 30.5]	22.2 [19.7, 24.7]	<0.001	<0.001
Kynurenine, µmol/l	1.6 [1.4, 1.9]	1.4 [1.2, 1.6]	<0.001	<0.001
Tryptophan, µmol/l	62.3 [55.4, 70.9]	63.0 [57.9, 68.9]	0.369	0.439
Quinolinic-to-kynurenic acid ratio	80.7 [65.7, 106.0]	83.6 [63.6, 99.8]	0.856	0.716*
Quinolinic acid, nmol/l	388.0 [312.0, 484.0]	351.5 [275.0, 437.8]	0.009	0.364*
Kynurenic acid, nmol/l	48.0 [37.3, 60.2]	42.9 [37.1, 49.5]	0.020	0.847*
3-Hydroxyanthranilic acid, nmol/l	44.7 [34.8, 59.7]	35.3 [29.5, 48.2]	<0.001	0.141*
Neopterin, nmol/l	16.7 [13.4, 21.4]	13.9 [12.1, 17.0]	<0.001	<0.001
hs-CRP, mg/dl	1.2 [0.6, 2.5]	0.9 [0.5, 1.7]	0.010	<0.001

Adjusted p-value: p-value after adjusting for HIV status, age, sex.
* these p-values have been further adjusted for kynurenine concentrations
Abbreviations: PWH, people with HIV ; hs-CRP, high sensitivity CRP; IQR, interquantile range

Table 3. Percent change in kynurenine-to-tryptophan ratio, quinolinic-to-kynurenic acid ratio, kynurenic acid, quinolinic acid, hs-CRP, and neopterin per 0.5-unit increase in waist-to-hip ratio in PWH

		PWH			
Change in % of outcome per 0.5 unit increase in waist-to-hip ratio	**Outcome**	**Crude β-coefficient [95% CI]**	**p-value**	**Adjusted β-coefficient [95% CI]**	**p-value**
	Kynurenine-to-tryptophan ratio	31 [17; 46]	<0.001	19 [5; 37]	0.009
	Quinolinic-to-kynurenic acid ratio	44 [22; 69]	<0.001	33 [8;66]	0.006
	Kynurenic acid	11 [-21;42]	0.505	-18 [-31; -3]	0.019
	Quinolinic acid	52 [30; 76]	<0.001	9 [-3; 34]	0.151
	hs-CRP	431 [232; 749]	<0.001	232 [80; 504]	<0.001
	Neopterin	19 [1; 37]	0.033	15 [-6; 40]	0.160

Abbreviations: PWH, people with HIV; hs-CRP, high sensitivity CRP.
Confounders included in multivariable models were age, sex, smoking, origin, BMI, and kynurenine (only when quinolinic-to-kynurenic acid ratio, kynurenic acid, and quinolinic acid included as dependent variables)

Figure 1. Association of kynurenic acid, quinolinic acid, and quinolinic-to-kynurenic acid ratio with hs-CRP and neopterin in PWH

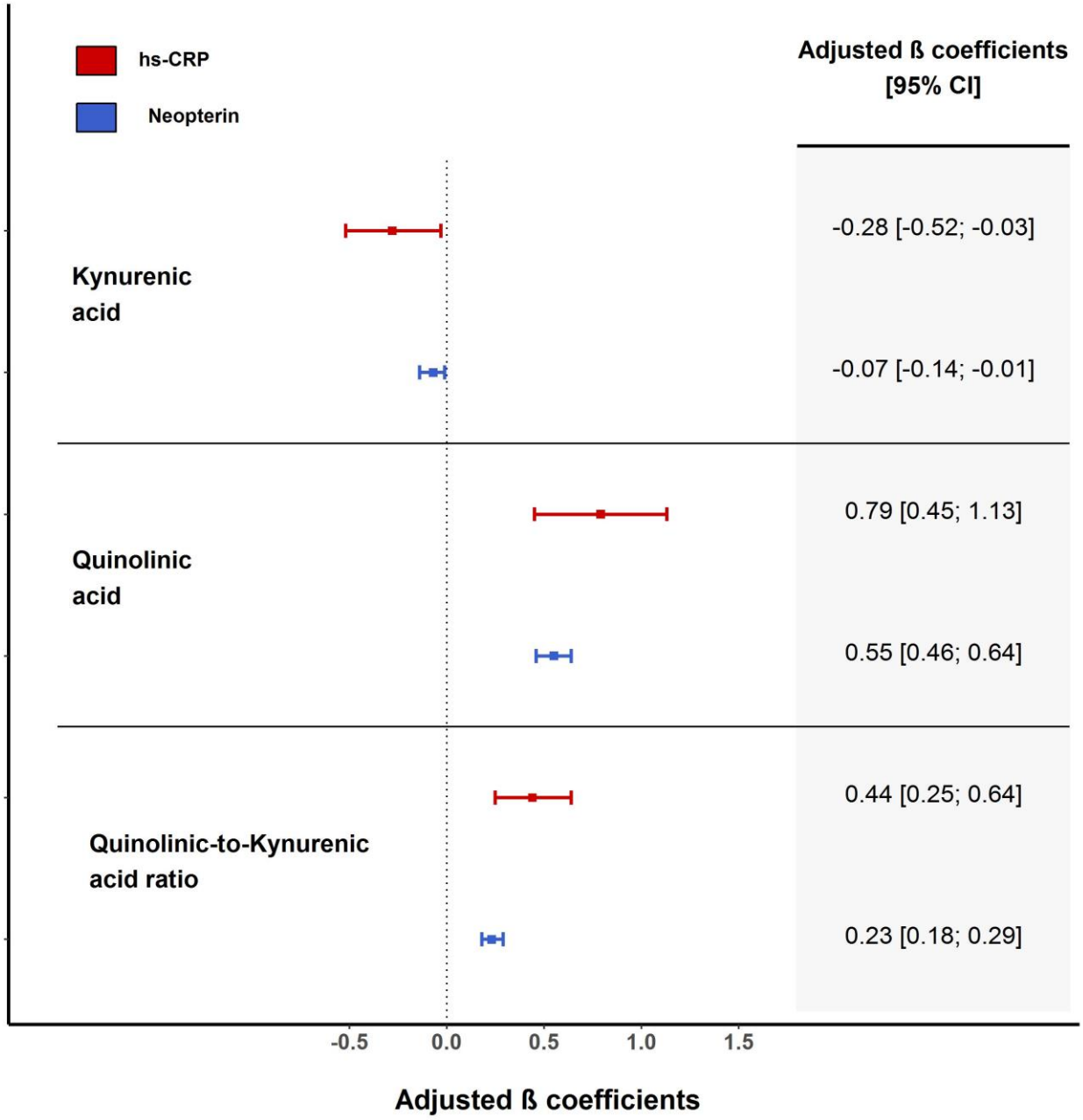

Figure 2. Change in lipids levels per 20% increase in kynurenine-to-tryptophan ratio and kynurenine metabolites after adjusting for confounders in people with HIV

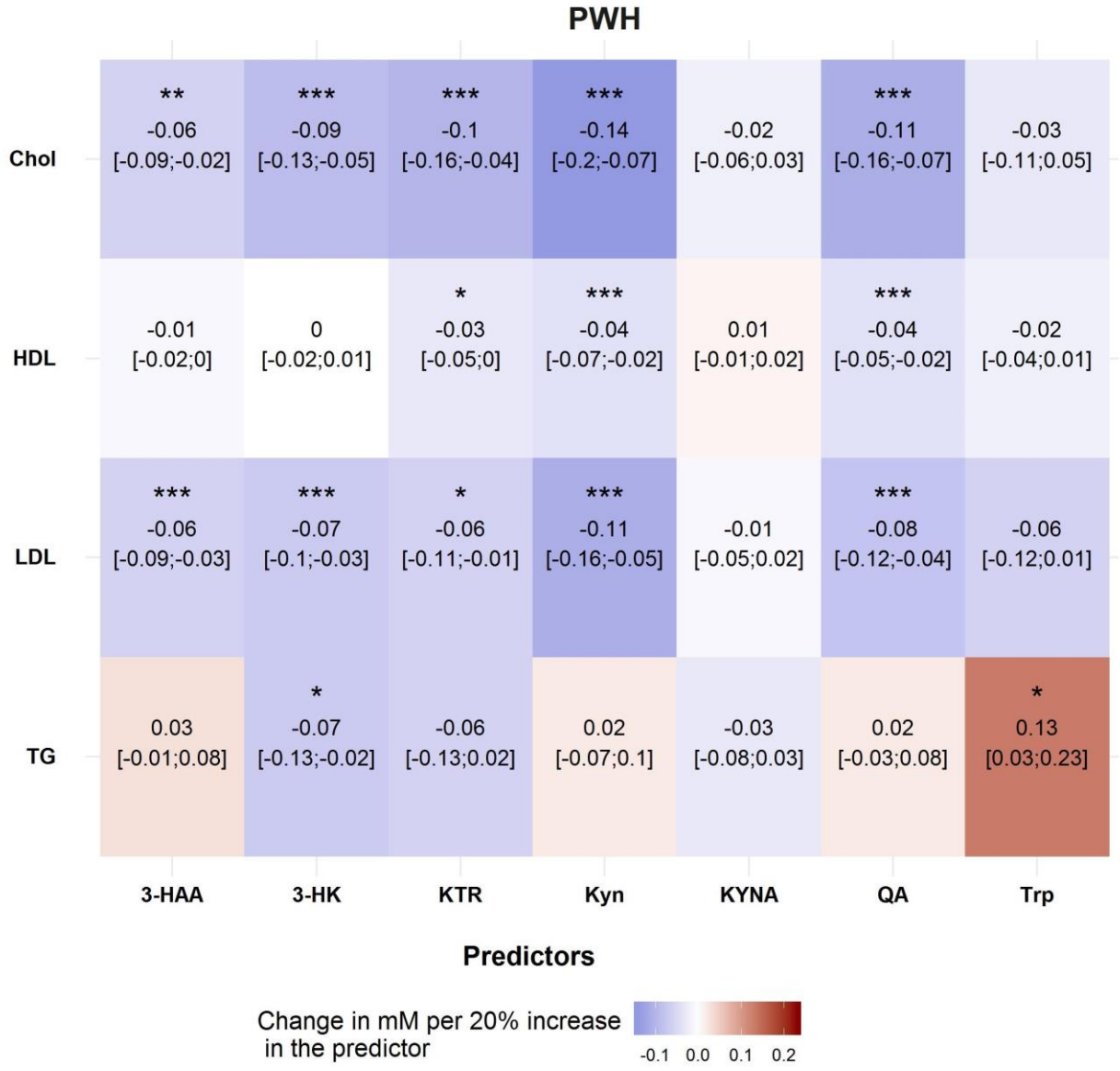

Figure legends

Figure 1. Association of kynurenic acid, quinolinic acid and quinolinic-to-kynurenic acid ratio with hs-CRP and neopterin concentrations. Results are shown as adjusted β coefficients. Confounders included in the models were: age, sex, smoking, origin, BMI, waist-to-hip ratio, and Kyn concentrations. Abbreviations: PWH, people with HIV; hs-CRP, high-sensitivity CRP; CI, confidence interval.

Figure 2. Association between lipids levels and 3-hydroxy-anthranilic acid, 3-hydroxykynurenine, kynurenine-to-tryptophan ratio, kynurenine, kynurenic acid, quinolinic acid, and tryptophan. β coefficients represent the mM change in the corresponding lipid level for 20% increase in the predictors. Confounders included in the models were age, sex, smoking, BMI, and anti-dyslipidemia treatment. P-value significance: *, < 0.05; **, < 0.01; ***, < 0.001 Abbreviations: PWH, people with HIV; 3-HAA, 3-hydroxy-anthranilic acid; 3-HK, 3-hydroxy-kynurenine; KTR, kynurenine-to-tryptophan ratio; Kyn, kynurenine; Trp, tryptophan.